REMARKS

The Specification has been amended to correct an inadvertent typographical error. Support is found in as-filed claim 8. Claim 1 has been amended to provide consistency between the preamble and the whereby clause, thus better claiming the invention. Claim 12 has been amended to delete an unnecessary presentation of an abbreviation. New claim 15, drawn to a composition in which the Amphotericin B is deaggregated, has been added. This new claim is supported by as-filed claim 1, and in the Specification. None of the amendments made herein constitutes the addition of new matter.

With the entry of the present Amendment, claims 1-15 are pending in this application.

The Rejection under 35 U.S.C. 112, second paragraph

Claims 4-5 and 12-15 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Applicant notes that the reference to claims 15 in the Office is an error in that only claims 1-14 were in this application at the time the Office Action was prepared.

The Patent Office has alleged that it is unclear whether the terms and expressions in parentheses are limitations of the claims.

Applicant respectfully notes that in claim 4, the expression in parentheses represents the ratio of chloroform and methanol in the solvent, as commonly expressed in the art. Thus, it can be interpreted as a limitation of this claim.

Applicant respectfully notes that in claim 12, the expression in parentheses

represents the abbreviation for poly(ethylene glycol)-1,2-di-stearoyl-phosphatidyl ethanolamine. As this is not recited in subsequent claims, this expression has been deleted from claim 12. It did not represent any limitation to the claim.

In view of the foregoing, Applicant respectfully submits that the claims, including 4-5 and 12-15, are definite and clear to one of ordinary skill in the art. Accordingly, the withdrawal of this rejection is respectfully requested.

The Rejections under 35 U.S.C. 103

Claims 1-14 were rejected under 35 U.S.C. 103 as allegedly unpatentable over Onyuksel (US Patent 6,217,886). Applicant respectfully traverses this rejection.

Onyuksel is said to disclose a method of preparing micelles containing the polyene compounds Amphotericin B (Am B) and Nystatin. The method is said to involve dissolving the water insoluble compound and the lipid conjugated polymer in an organic solvent, removing the organic solvent and hydrating the lipid film to form micelles. The Patent Office has noted that the reference does not provide the conditions of temperature and pressure under which the organic solvent is removed before hydration nor are the ratios of amphotericin B to PEG-DSPE taught. Furthermore, dextrose is said to be taught by Onyuksel as a cryopreservative. The Patent Office has concluded that it would have been obvious to manipulate the basic teachings of the cited patent to obtain micelles with the desired amounts of the active agents.

Applicant has reviewed the cited Onyuksel reference and note that, in general and in the specifically exemplified methods disclosed therein, the PEG-DSPE is dissolved in an organic solvent (i.e., chloroform), dried to prepare micelles and then **after hydration**, the hydrated micelle-containing material is mixed with the biologically

active agent. It is specified in Onyuksel's claim 1 that the biologically active material becomes associated with the sterically stabilized micelles. There is little disclosure related to making micelles with a different strategy, and that limited disclosure for mixing polymer and active agent does not provide for the combination of Am B with polymer.

Onyuksel does not disclose that a polyene antibiotic-containing antibiotic preparation (made by the method of Onyuksel) would contain deaggregated antibiotic (for example, Am B). The present invention relies on **deaggregated** Am B as a means for minimizing hemolytic activity while providing a soluble formulation of this difficult-to-administer therapeutic agent. The presently claimed preparation process allows for the association of the polyene antibiotic with PEG-DSPE in a way which prevents aggregation of antibiotic when hydrated, thus minimizing its toxicity (as measured by hemolysis). Thus the cited Onyuksel actually teaches away from the present claimed method for providing a polyene antibiotic formulation which is soluble and has reduced toxicity (due to deaggregated state) as compared to known prior art compositions, either with respect to the polymer carrier or aggregated polyene antibiotic.

There is nothing in the cited reference which would lead to a reasonable likelihood of success in the current claimed invention, in that a different strategy is employed and there was no teaching of a need for a different strategy for formulations or a need for a deaggregated form of drug. There is nothing on the record which would lead one of ordinary skill in the art to believe that the instant claimed process and that of Onyuksel were interchangeable.

Moreover, claim 1 contains a limitation as to the temperature for hydration of the dried layer (in step (b), adding water at a temperature from 25°C to 80°C to the drug-polymer film) which does not appear to be taught or suggested in the cited reference. Thus, it appears that the cited reference does not teach or suggest this aspect of the

present claimed invention.

Furthermore, the present Specification teaches the production of micelles in which the polyene antibiotic is deaggregated. This does not appear to be taught by the cited Onyuksel reference, and Applicant respectfully maintains that this is an advantage of the present invention (aggregated Am B, for example, is toxic).

Finally, Applicant notes that the cited portion of Onyuksel relates to the preparation of a **crystalline** product or a sterically stabilized micelle preparation (col. 14, lines 15-47, claims 7-11 and 31). Onyuksel acknowledges that the "crystalline product of the method is essentially a micelle-encased **aggregate** of the **insoluble** compound which is densely packed and crystallized" (column 14, lines 12-15; emphasis added). The present invention, as set forth in claims 1-14, by contrast, does not relate to a crystalline product, but rather relates to micelles which contain a deaggregated product, including new claim 15 which specifies the deaggregated state of the Am B. In addition, claims 12-15 specify the ratio of amphiphilic polymer and Am B.

Claims 1-15 are not rendered obvious by the cited reference because Onyuksel fails to teach, enable or suggest all the limitations of the instant claims, in particular for a method of making micelles comprising a deaggregated polyene antibiotic.

In view of the foregoing, Applicant respectfully submits that there has been no *prima facie* case for obviousness made out, and the withdrawal of the rejection is requested.

Claims 1-11 were rejected under 35 U.S.C. 103 as allegedly unpatentable over Moribe et al. (1998). Applicant respectfully traverses this rejection.

Moribe is said to teach a method of preparing **liposomes** containing polyene compound, Am B. The method is said to involve dissolving the water insoluble compound and the lipid conjugated to a water soluble polymer in organic solvents (chloroform, methanol), removing the organic solvents and hydrating the lipid film to form liposomes (page 1738). Moribe is said to lack pressure and temperature conditions under which the organic solvents are removed from the PEG-DSPE solution before hydrating it. However, in the absence of unexpected results, evaporation of solvents using different temperature and pressure conditions is deemed to be a manipulable parameter in the highly developed chemical sciences. The amounts of Am B and PEG-DSPE appear to be in the broad ratios claimed in claim I. Moribe is also said to teach the amount of Am B encapsulated increased with the amount of PEG-DSPE used and with PEG molecular weight, and therefore it was deemed obvious to vary the amounts of the PEG-DSPE and the molecular weight of PEG if higher amounts of encapsulated Am B are desired.

In contrast to the present invention as claimed with the preparation of micellar compositions with the polyene antibiotic and the polymer, Applicant respectfully notes that the cited Moribe reference actually teaches the complexing of Am B with DSPE-PEG and **then** encapsulating it into DPPC/cholesterol **liposomes**. Liposomes are fundamentally different than micelles. Liposomes are significantly larger structures than micelles, and in general, they are notoriously less stable than micelles in aqueous environments. The present claims do not recite the incorporation of DPPC/cholesterol with DSPE-PEG and a deaggregated polyene antibiotic. There is nothing in the cited reference that would suggest that deaggregated polyene antibiotic, including Am B, could be made into micellar structures, or that DPPC/cholesterol was not or would not be necessary to incorporate into a composition providing **deaggregated** polyene. In addition, there is no teaching or suggestion in the cited Moribe reference of the temperature range for the hydration of dried material, as taught in the present Specification and recited in claim 1, and in another range, in claim 6.

In view of the foregoing, Applicant respectfully submits that there has been no *prima facie* case for obviousness made out, and the withdrawal of the rejection is requested.

Claims 1-14 were rejected under 35 U.S.C. 103 as allegedly unpatentable over Allen (2004/0013717) by itself or Allen in view of Yu et al. (1998). Applicant respectfully traverses this rejection.

Allen is said to teach micellar formulations containing PEG-DSPE to deliver any chemical or biologically active agent. The method of preparing was said to involve dissolving the active agent and the phospholipid in an organic solvent, evaporation using a rotary evaporator increasing the vacuum in 25 mbar increments and hydrating the lipid film to form the micelles. The compositions could be freeze-dried in the presence of a cryoprotectant such as a saccharide and rehydrated before use. The weight of PEG is between 1000 and 10,000. The Patent Office concluded that it would have been obvious to use any active agent including Am B with a reasonable likelihood of success since Allen taught allegedly general applicability.

Applicant does not see that the cited Allen reference, which aspirationally suggests any chemically or biologically active molecule, and more specifically, a photosynthesizing agent, to be incorporated into micelles, actually suggests the use of a polyene antibiotic or why one of ordinary skill in the art would choose this particular strategy from the myriad of strategies for formulating such antibiotics known to the art. Many references relating to strategies for providing polyene antibiotics, including Am B, are known to the art. Accordingly, Applicant respectfully submits that there is no *prima facie* case for obviousness made out, and the withdrawal of the rejection is respectfully requested.

Yu is said to teach polymeric micelles for delivery of Am B, specifically where the polymer was a PEG derivative of benzyl-aspartic acid, and their use to reduce hemolysis by Am B.

The Patent Office has alleged that one would have been motivated to use Am B in the micelles of Allen with a reasonable expectation of success since the cited Yu reference showed the knowledge of the art of Am B and polymeric micelles to reduce the hemolytic activity of Am B. Alternatively, the use of PEG-DSPE instead of PEG-block-β-benzyl-aspartate would allegedly have been obvious to one of ordinary skill in the art since the reference of Allen showed that PEG-DSPE also formed micelles and such micelles could be used for delivery of active agents. The Patent Office concedes that Allen did not specifically teach dextrose as saccharide but has alleged the use of any saccharide would have been obvious to one of ordinary skill in the art with a reasonable expectation of success.

Allen focuses on photosensitizers, and suggests the use of "any chemically or biologically active agent". This represents a vastly broad class of molecules, of which the polyene antibiotics are a small class. Notably, Allen does not specifically teach antibiotics. Allen does not appear to make any statements or teachings concerning temperatures for the hydration step, as specified in the present claims.

The cited Yu reference has provided an alternative strategy to that claimed for formulating Am B. It teaches a different polymeric material (PEG-poly β-benzyl-L-aspartate), and it teaches a different method (dialysis) for the preparation of micelles. Thus, it leads away from the present claimed invention, as there is no indication that various components such as the polymer are interchangeable. In addition, it does not provide any teaching or suggestion relating to the temperature range for a hydration step, as in the present claimed invention.

Applicant respectfully states that the combination of the Allen and the Yu references would not lead to the present claimed invention. Also, there is not suggestion or motivation for one to combine these two references, absent the impermissible use of hindsight. Certainly there was no teaching of the temperature range in step (c) of claim 1.

Furthermore, the Yu reference does not appear to teach or suggest any deficiency of the compositions taught therein; accordingly, on that basis, there would be no motivation to seek improvement, or to combine the teachings of Yu with the cited Allen reference.

With respect to the composition claims (now claims 12-15), there is no teaching of micelles containing Am B in the cited Allen reference, and in Yu, it is taught that compositions should be formulated with a PEG-block-poly(β-benzyl-aspartate) and prepared with a dialysis step. In addition, neither cited reference teaches or suggests the deaggregated state of Am B in the claimed compositions of claims 12-15, nor do these references teach or suggest the particular ratio of components as recited in the instant claims.

It is Applicant's position that these references, alone or in combination, did not provide the requisite teachings, motivation or probability of success to support a conclusion of obviousness. In combination they might be asserted to yield a PEG-Asp preparation containing a photoactive agent. Such a combination does not plausibly have relevance to a polyene antibiotic in combination with a PEG-phospholipid, as set forth in the present claims, and there would have still been lacking the recited temperature range in the method steps.

In sum, Applicant respectfully maintains that the present invention as claimed is

not obvious over the cited references, and the rejection should be withdrawn.

Claim 14 was rejected under 35 U.S.C. 103 as allegedly unpatentable over Onyuksel (6,217,886) or Allen (2004/0013717) by itself or in view of Yu et all (1998) or vice versa as set forth above in view of McShane (6,906,042). Applicant respectfully traverses this rejection.

The Patent Office has characterized the cited McShane patent as disclosing micellar formulations rehydrated with dextrose solution, which is suitable for intravenous administrations.

The disclosure of McShane appears to relate to micelles having a very specific compound of Formula A. The structure of Formula A bears essentially no relationship to any component of the micelles formed in the claimed methods and compositions of the instant application. Thus, apart from the common use of the term "micelles" and the mention of "dextrose", the disclosure of McShane is not relevant to the patentability of the present claimed invention. McShane does not appear to disclose antibiotics, let alone polyene antibiotics. There is no specific basis for any teaching suggestion or motivation to combine McShane with any of the other cited references.

The other references have been discussed above, and Applicant has made the case for patentability of the claimed methods for preparing micellar compositions containing Am B. It is the deaggregated state of the polyene antibiotic, which is a important feature of the present claimed invention, which follows from carrying out the claimed method steps, including the temperature range over which the hydration step is performed, and with respect to Onyuksel, the steps for preparation of the micellar compositions which are distinguished from the present methods. It was a significant achievement to produce solubilized, deaggregated Am B preparations which were not characterized by relatively high levels of solubilizing agent to drug, i.e., PEG-DSPE, as

was the case in certain prior art formulations, e.g., Barwicz et al. (1992) Antimicrobial Agents and Chemotherapy 36:2310-2315, already of record. It is Applicant's position that the present claimed methods and ratio of polymer to drug lead to the improved properties of those compositions.

Accordingly, no *prima facie* case for obviousness of the present invention has been made out, and the withdrawal of the rejection is respectfully requested.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time (three months) and the Patent Office is authorized to charge the amount of $510.00 to Deposit Account No. 07-1969. It is believed that this response does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If the amount submitted is incorrect, however, please deduct as necessary from Deposit Account No. 07-1969.

Respectfully submitted,

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